## REMARKS

### I. Status of Claims

Claims 1-6, 22, and 23 are under examination in this application. Claims 7-21 are withdrawn from the consideration by the Examiner because they are directed to non-elected subject matter.

In the present amendment, claims 1-6 and 23 have been amended to more appropriately claim the invention, and to correct informalities. In addition, new claims 24-28 have been added to more appropriately claim the invention. Support for new claims 24-28 can be found in the original claims 1-6, 22, and 23 and the specification of the present invention as originally filed on February 13, 2002. Specifically, for example, support for claim 24 can be found in paragraph [074], for claim 25 in paragraphs [068] - [070], for claims 26 in paragraphs [080] and [081], for claim 27 in paragraph [0346], and for claim 28 in paragraph [0215], of the specification of the present invention as originally filed on February 13, 2002.

Applicants have not introduced any new matter by the amendment, nor are any estoppels intended thereby. Further, the amendment does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner.

### II. Election/Restriction Requirement

In the Office Action, at page 2, the Examiner requires restriction under 35 U.S.C. § 121 among the following Groups:

Group I. Claims 1-6, 22, and 23, drawn to compounds of formula I and their pharmaceutical compositions;

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Group II. Claims 7-13, drawn to a method of stimulating the expression of endothelial NO-synthase in a mammal; and

Group III. Claims 14-21, drawn to a method of treating a mammal suffering from a disease as recited, for example, in claim 14.

Applicants respectfully traverse the restriction requirement for at least the following reason. However, to be fully responsive, Applicants provisionally elect, with traverse, the subject matter of Group I, claims 1-6, 22, and 23, for prosecution on the merits.

For a restriction requirement to be proper, the Examiner bears burden of proof to show that "(A) the process of using as claimed can be practiced with another materially different product; or (B) the product as claimed can be used in a materially different process." M.P.E.P. § 806.05(h) (8th ed., August 2001). However, the Examiner has not met his burden, because he merely contended that "[i]n the instant case[,] the diseases embraced by the method of use claims are known to be treated by other compounds[,]" (Office Action, page 2) without providing any exemplary evidence of "another materially different product" as required by the M.P.E.P. Therefore, Applicants respectfully request claims of Groups I-III be examined together.

At least, Applicants respectfully submit that examinining the claims of Groups II and III together would not impose a serious burden, because the Examiner has not shown separate classification for Groups II and III. *See Id.* § 803. In fact, both Groups II and III are listed as falling within "class 514, subclass[es] 183+, 613+, etc." Office Action, page 2. Therefore, by examining the claims of Group II in the cited class and subclasses, the claims of Group III could also be examined.

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Accordingly, Applicants respectfully request that the Examiner withdraw the restriction requirement and examine claims of Groups I-III together.

## III. Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1-6, 22, and 23 under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." *Id.* at page 3. Specifically, the Examiner alleged that, "[i]n claim 1, the phrase 'An acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine according to the general formula (I)' renders the claim indefinite because one cannot say what else is intended." *Id.* The Examiner suggested change this phrase to "A compound of formula (I)." *Id.*

Although Applicants disagree with the Examiner's rejection, to facilitate the prosecution of the present invention, Applicants have amended the claims according to the Examiner's suggestion, which are shown in the Amendments to the Claims as set forth above. Accordingly, Applicants respectfully request this rejection be withdrawn.

## IV. Objection under 37 C.F.R. § 1.75

The Examiner further objected to claim 22 under 37 C.F.R. § 1.75 "as being a substantial duplicate of claim 23." *Id.* at page 4 (citing M.P.E.P. § 706.03(k)). Applicants respectfully disagree for at least the following reason.

Contrary to the Examiner's allegation, claim 22 and claim 23 are not duplicates, nor are they close enough to cover the same thing. Claim 22 recites a pharmaceutical preparation, which can be in any form; while claim 23 is dependent on claim 22 and

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recites a pharmaceutical preparation in a specific form chosen from various forms listed therein. Therefore, the scope of claim 23 is narrower than that of claim 22. "[A] mere difference in scope between claims has been held to be enough." M.P.E.P. § 706.03(k). Accordingly, Applicants respectfully request this objection be withdrawn.

## V. Rejection under 35 U.S.C. § 103(a)

The Examiner further rejected claims 1-6 under 35 U.S.C. § 103(a) "as being unpatentable over Vejdelek et al. (Collection of Czechoslovak Chemical Communications (1971), 36(4), 1611-23)" ("*Vejdelek*"). Office Action, page 4. Specifically, the Examiner relied on the compound of RN 35047-56-4 in a single summary page of the Caplus search he conducted (*i.e.*, the page attached to the Office Action immediately after the signed PTO form 1449), and alleged that the claims of the present invention "differ by requiring the -NH-C(O)-$R^5$ group at the 2-position over the 1-position of the prior art compound[,]" so the compounds claimed in the present invention are ring position isomers of the *Vejdelek*'s compound. *Id.* The Examiner further alleged that "[p]osition isomers are well established as being prima facie structurally obvious." *Id.* at pages 4-5 (citation omitted). Applicants respectfully disagree for at least the following reasons.

The M.P.E.P. instructs that "[i]somers . . . are <u>not</u> necessarily considered equivalent by chemists skilled in the art and therefore are <u>not</u> necessarily suggestive of each other." M.P.E.P. § 2144.09 (citing *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950)) (emphasis added). The M.P.E.P. further instructs that (1) if the prior art reference does not teach any specific or significant utility for the disclosed compounds, or (2) if the prior

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art reference merely discloses compounds as intermediates in the production of a final product, the prior art reference cannot render the claimed structural isomers obvious because there is no requisite suggestion or motivation. *Id.*

Here, in this case, to fully understand what has been disclosed in *Vejdelek*, Applicants do not believe the single summary page from the Examiner's Caplus search is sufficient. Therefore, Applicants enclose a copy of *Vejdelek* in its complete version for Examiner's convenience.

*Vejdelek* discloses various benzocycloheptenes and heterocyclic analogues. However, only compounds XVIII, XIX, XX, XXI, and XXII disclosed on page 1613 of *Vejdelek* may arguably be structural isomers of the compounds claimed in the present invention, wherein compound XXII is the compound of RN 35047-56-4 that the Examiner relied on.

Among these compounds, compounds XVIII and XIX are intermediates. *See Vejdelek,* page 1612, lines 4-9.

> [I]f the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not have been motivated to stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses.

M.P.E.P. § 2144.09 (citing *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)). In addition, compounds XX, XXI, and XXII do not have any specific or significant positive pharmaceutical effects. *See Vejdelek,* page 1615, Table I.

> If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary

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> skill in the art to make the reference compounds, much less any structurally related compounds.

M.P.E.P. § 2144.09 (citing *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971)). Therefore, there is no requisite suggestion or motivation to modify *Vejdelek* to reach the presently claimed invention according to the M.P.E.P.

More importantly, *Vejdelek* teaches that compound XXI "[c]auses pupil myosis and slightly increases blood sugar level in rats." Page 1615, Table I. Therefore, *Vejdelek* clearly teaches away from the presently claimed invention, negating reasonable expectation of success, if there is any.

Accordingly, Applicants respectfully request this rejection be withdrawn.

## VI. Conclusion

In view of the foregoing claim amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application, and the timely allowance of the pending claims.

If the Examiner believes a telephone conference could be useful in resolving any outstanding issues, he is respectfully urged to contact Applicant's undersigned counsel at 202-408-4218.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 26, 2003

By: _____
Ningling Wang
Reg. No. 52,412

Enclosure:
Collection of Czechoslovak Chemical Communications 36(4), pp. 1611-23 (1971).

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Volume 36

4

April
1971

# BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. I.

## N-SUBSTITUTED DERIVATIVES OF 5-AMINO-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENE AND SOME OTHER COMPOUNDS

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Received April 27th, 1970

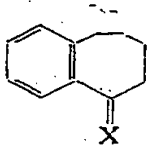
6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-one (*I*) was used for the preparation, mostly *via* 5-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XII*), of a number of amines and amides (*XIII*—*XXVI*). Ketone *I* reacted with 3-dimethylaminopropylmagnesium chloride to yield the aminoalcohol *V* and this was dehydrated to the olefinic amine *VI*. In connection with attempts to cyclize 2,5-diphenylvaleric acid (*XXVII*) some nitrogen derivatives of this acid *XXIX*—*XXXI* were prepared. Pharmacological screening demonstrated a hypotensive effect with a number of products (especially *V*, *VI*, *XIV*, *XXV*, *XXVI*, *XXIX* and *XXX*), while *VI* and *XV* were diuretically active and *XXIX* was also a local anaesthetic and a spasmolytic.

During the past 15 years, seven-membered rings have played an ever-increasing role in pharmaceutical chemistry. This resulted in contributing to the development of the chemistry of these homocyclic as well as heterocyclic compounds and in the discovery of a number of valuable pharmaceutical preparations with mostly neurotropic and psychotropic activity. Particularly typical in this respect are amines derived from dibenzo[*a*,*d*]cycloheptene and its most varied heterocyclic analogues; some work in this area has been also done by this working team[1,2]. The discovery of psychotropic activity of derivatives of 1,4-benzodiazepin[3,4] partly resulted in a shift of interest to bicyclic compounds with a seven-membered ring which may be collectively designated as derivatives of benzocycloheptene and its heterocyclic analogues. Our recent work with the groups of derivatives of 1-benzothiepin[5] and 3-benzazepin[6], as well as some further synthetic attempts[7,8] indicate that our research group also followed the trend. The work is beginning to increase in scope and to acquire a systematic character and hence a separated series will be devoted to it.

The tetrahydro-derivative of the basic skeleton, *i.e.* 6,7,8,9-tetrahydro-5*H*-benzocycloheptene, is interesting as a carrier system analogous to indane and tetralin. From this point of view we devoted some attention to it during synthesis of potential antihistaminics[9], spasmolytics[10] and local anaesthetics[11]. The focus of the present work lies in the synthesis of N-substituted derivatives of 5-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene. In this direction we followed the same path as the team of Anand[12] which was realized after the termination of the present experiments.

The key intermediate of the work was 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one (*I*), readily available through cyclization of 5-phenylvaleric acid with polyphosphoric acid[13]. Amine *XII* was prepared from *I* *via* the oxime[14] by reduction with lithium aluminium hydride in ether[15] or with sodium in ethanol. Crude carbamate *XVIII* was obtained in the reaction of the amine *XII* with ethyl chloroformate and was then reduced with lithium aluminium hydride in tetrahydrofuran to the methylamino derivative *XIII*. The same compound was prepared by reduction of the formamido derivative *XIX* obtained in the reaction of 6,7-dihydro-5*H*-benzocycloheptene (*X*)[16] with hydrogen cyanide according to Ritter's reaction. Methylation of the methylamino derivative *XIII* with formaldehyde and formic acid yielded the dimethylamino derivative *XXIII*. The formamide *XIX* and the amines *XIII* and *XXIII* were also prepared by Anand and others[12] but using different procedures. The amide *XX* obtained by acetylation of the amine *XII* was converted by lithium aluminium hydride in tetrahydrofuran to the ethylamino derivative *XIV*. The corresponding diethylamino derivative *XXIV* was obtained as a minor product of the substitution reaction of crude 5-chloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*III*)[17,18] with diethylamine. The principal product of this reaction was the hydrocarbon *X* which was prepared planfully by dehydrochlorination of the chloro-derivative *III* with the aid of collidine and which was also obtained as the single product of treating 5-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*) with dimethylcarbamyl chloride[16,18,19].

Substitution reaction of the chloride *III* with 1-methylpiperazine yielded the methylpiperazine derivative *XXV*[12]; here, too, elimination to the hydrocarbon *X* predominated. Alkylation of the amine *XII* with 3,3-diphenylpropyl bromide[20] yielded



*I*, X = O

*II*, X = CHOH

*III*, X = CHCl

*IV*, X = $NC_6H_5$

*V*, X = $C(OH)(CH_2)_3N(CH_3)_3$

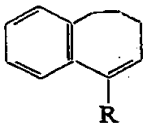
*VI*, X = $CH(CH_2)_2N(CH_3)_2$

*VII*, X = $C(OH)C_6H_5$

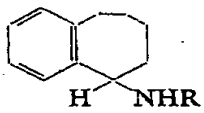
*VIII*, X = $C(O(CH_2)_2N(CH_3)_2)C_6H_5$

*IX*, X = $CHC_6H_5$

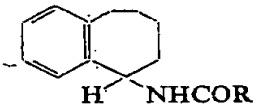
the amine *XV* which is a distant analogue of "prenylamine"[21]. Similarly, the reaction of amine *XII* with 1-(1-naphthoxy)-2,3-epoxypropane[22] yielded the aminoalcohol *XVI* which is an analogue of propranolol[23]. Acylation of amine *XII* with phenylacetyl chloride and 3,4,5-trimethoxybenzoyl chloride resulted in amides *XXI* and *XXII*. Reaction of the ketone *I* with aniline in the presence of zinc chloride (method according to[24]) yielded the anil *IV* which was reduced with lithium aluminium hydride in ether to 5-anilino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XVII*). Subsequent alkylation with 2-dimethylaminoethyl chloride in the presence of sodium amide resulted in the tertiary amine *XXVI* which is a cyclic analogue of the antihistaminic "phenbenzamine"[25] and a homologue of the previously described indane derivative[26].



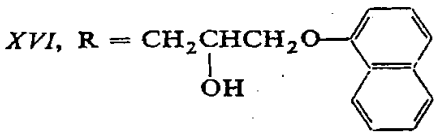
*X*, R = H
*XI*, R = $C_6H_5$



*XII*, R = H
*XIII*, R = $CH_3$
*XIV*, R = $C_2H_5$
*XV*, R = $CH_2CH_2CH(C_6H_5)_2$

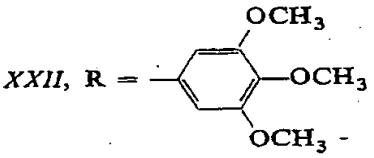


*XVIII*, R = $OC_2H_5$
*XIX*, R = H
*XX*, R = $CH_3$
*XXI*, R = $CH_2C_6H_5$



*XVI*, R = $CH_2CHCH_2O$ (OH)

*XVII*, R = $C_6H_5$



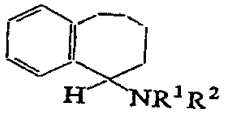
*XXII*, R = 3,4,5-trimethoxyphenyl

Reaction of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one (*I*) with 3-dimethylaminopropylmagnesium chloride[27] in tetrahydrofuran produced the aminoalcohol *V* which was dehydrated by heating with dilute hydrochloric acid. On the basis of its UV spectrum (for a comparison see[19]) we ascribe to the product the structure of the olefinic base *VI* with the exocyclic double bond (the problem of geometric isomerism remaining unsolved). Anand and coworkers[12] described the preparation of the analogous diethylamino derivative.

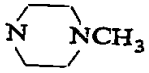
For a better characterization of the previously prepared 5-(2-dimethylaminoethoxy)-5-phenyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VIII*) (it had been prepared only as a methiodide[9]) and to make possible a more detailed pharmacological testing its preparation was repeated. Reaction of ketone *I* with phenylmagnesium bromide yielded, not in full agreement with previous data[9,19,28], a mixture of alcohol *VII* (yield about 33%) and of the dehydrated product *XI* (22%) which was readily separated on the basis of fine crystallization ability of the alcohol *VII*. This alcohol was then converted by the conventional procedure[9] to the basic ether *VIII* which

was now prepared in the form of crystalline hydrogen maleate. Hydrogenation of the olefin *XI* on platinum yielded 5-phenyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IX*).

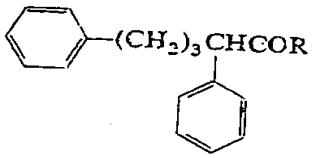
As a suitable intermediate product for further work we selected the heterofore undescribed 6-phenyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one which, in analogy to ketone *I*, should result from cyclization of 2,5-diphenylvaleric acid (*XXVII*)[29]. However, at temperatures below 100°C (*i.e.* under conditions when 5-phenylvaleric acid will cyclize smoothly[13]) the acid *XXVII* will practically not react with polyphosphoric acid. The acid chloride *XXVIII* reacts with aluminium chloride in carbon disulfide but the product is polymeric and insoluble in organic solvents. The acid *XXVII* was induced to react with polyphosphoric acid only at 140—160°C. The mixture formed was distilled to yield directly 40% of 1-phenyltetralin (*XXXII*) identified by comparison with an authentic product[30]. After this work had been terminated, Khanna and Anand[31] published the same reaction (without reporting the used temperature) which yielded 1-phenyltetralin as the principal product. Crystallization and chromatography of the distillation residue after 1-phenyltetralin yielded two further crystalline products which have not been identified (colourless hydrocarbon $C_{17}H_{14}$ with m.p. of 138—139°C and a yellowish oxygen-containing compound $C_{34}H_{30}O$? melting at 135—136°C, $\nu$ 1670 $cm^{-1}$). The desired ketone has not been detected, in agreement with the paper cited[31].

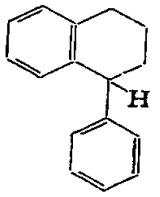


*XXIII*, $R^1 = R^2 = CH_3$
*XXIV*, $R^1 = R^2 = C_2H_5$

*XXV*, $NR^1R^2 =$ 

*XXVI*, $R^1 = C_6H_5$, $R^2 = CH_2CH_2N(CH_3)_2$





*XXVII*, R = OH
*XXVIII*, R = Cl

*XXIX*, $R = O(CH_2)_2N(C_2H_5)_2$
*XXX*, $R = N(C_2H_5)_2$

*XXXII*

*XXXI*, $R = NH(CH_2)_3N$ 

The chloride of 2,5-diphenylvaleric acid *XXVIII* was then converted to the 2-diethylaminoethyl ester (*XXIX*), diethylamide (*XXX*) and 3-morpholinopropylamide (*XXXI*) which were considered as potentially interesting from the pharmacological point of view.

TABLE I

Pharmacological Properties of Newly Synthesized Compounds

| Compound | $LD_{50}$ mg/kg | Application dose, mg/kg | Effects observed |
|---|---|---|---|
| *II* | 2 500 | *p.o.* 300 | No pronounced effects. |
| *V* | 60 | *i.v.* 12 | Causes a slight and prolonged drop of blood pressure (rats in pentobarbital narcosis); at a dose of 50 μg it has a negative inotropic and chronotropic effect on isolated rabbit auricle. |
| *VI* | 45 | *i.v.* 9 | Local anaesthetic effect (infiltration anaesthesia in guinea pigs) weaker than procaine. Causes slight and prolonged drop of blood pressure; indication of diuretic (mice) and vasodilatory (mice) effect. |
| *VIII* | 44·5 | *i.v.* | No central depressant effect (rotating rod, mice) and no antireserpine effect (ptosis, mice); in the histamine aerosol test in guinea pigs it is practically ineffective at a dose of 5 mg/kg *i.p.* It has no antiserotonin effect on rats *in vivo*. |
| *XII* | 50 | *i.v.* 10 | Local anaesthetic effect weaker than procaine. It brings about brief drops of blood pressure (*cf.*[12]). |
| *XIV* | 40 | *i.v.* 8 | Causes pupil myosis (mice), decreases briefly the blood pressure and increases heart inotropy with slowing down of frequency. |
| *XV* | 2 500 | *p.o.* 300 | Indication of diuretic and anti-inflammatory effect (kaolin edema in rats). |
| *XVI* | — | *p.o.* — | At a dose of 150 mg/kg it decreases slightly, at a dose of 300 mg/kg pronouncedly, the blood pressure of *Macacus rhesus*. The effect sets in 1 h after application and persists for 3—4 h. With anaesthetized rats it has a hypotensive effect at 600 mg/kg, the drop persisting for 1—1·5 h. |
| *XX* | 2 000 | *p.o.* 300 | No pronounced effects. |
| *XXI* | 1 000 | *p.o.* 200 | Causes pupil myosis and slightly increases blood sugar level in rats. |
| *XXII* | 2 500 | *p.o.* 300 | No pronounced effects. |
| *XXIII* | 40 | *i.v.* 8 | Causes slight drop of blood pressure and increases heart inotropy. |
| *XXV* | 50 | *i.v.* 10 | Causes profound and prolonged drop of blood pressure and at a dose of 50 μg shows a negatively inotropic effect on isolated heart auricle, also decreasing frequency. |

TABLE I (*continued*)

| Compound | $LD_{50}$ mg/kg | Application dose, mg/kg | Effects observed |
|---|---|---|---|
| *XXVI* | 100 | *i.v.* 20 | Pronouncedly decreases blood pressure in rats in urethane narcosis (by 25—35% within 15—20 min). |
| *XXIX* | 35 | *i.v.* 7 | Shows a pronounced prolonged drop of blood pressure, prolonged bradycardia and extension of the QRS complex on the ECG. Inhibits contractions of isolated rat duodenum caused by barium chloride and by acetylcholine. Causes pupil myosis. Shows indications of hypoglycemic effect. At a concentration of 0·5—1% it shows a more pronounced local anaesthetic effect on rabbit cornea than cocaine. |
| *XXX* | 1 500 | *p.o.* 300 | Insignificantly decreases blood pressure (rats) and body temperature (rats). |
| *XXXI* | 37·5 | *i.v.* 7 | Causes a prolonged decrease of blood pressure, pronounced prolonged bradycardia and an extension and decrease of the QRS complex on the ECG. Inhibits heart inotropy. In slight hypertensive (DOCA) unanaesthetized rats a dose of 20 mg/kg *p.o.* causes a drop of blood pressure by 15—25% within 2—4 h. |

A greater part of our products were evaluated by the usual methods of pharmacological screening. The results obtained are summarized in Table I containing the acute toxicity ($LD_{50}$) for mice and then the dose used for most *in vivo* tests. Compounds *V*, *VI* and *VIII* were tested as hydrogen maleates, compounds *XII*, *XIV—XVI*, *XXIII* and *XXIX* as hydrochlorides. Compound *XXV* was tested as dihydrochloride and compound *XXVI* as dihydrochloride monohydrate.

## EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block. The samples were dried for 8 h in oil-pump vacuum (about 0·2 Torr) over phosphorus pentoxide at a temperature adequate to the melting point of the substance (at most 100°C). The UV spectra were recorded on a Unicam SP 700 spectrophotometer, the IR spectra either on a Unicam SP 200G or on a Zeiss UR-10 spectrophotometer.

### 5-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XII*)

A solution of 90 g oxime of the ketone *I* (m.p. 105°C) (ref.[14]) in 500 ml ethanol was added dropwise over a period of 25 min to 300 g sodium. Within subsequent 30 min 750 ml ethanol were added dropwise and the mixture was then refluxed for 7·5 h while adding gradually 1 500 ml etha-

nol until all the sodium was dissolved. After cooling, 300 ml water were first added dropwise and the mixture was steam-distilled, the distillate being collected in a mixture of 300 ml water and 140 ml concentrated hydrochloric acid. The distillate (6 liters) was evaporated at reduced temperature practically to dryness and the precipitated hydrochloride (88·5 g) was filtered; m.p. 265—268°C (ethanol–ether). The product is identical with the compound prepared by reduction of the oxime with lithium aluminium hydride (m.p. of the hydrochloride was reported as 267 to 270°C) (ref.[15]). The base liberated from the hydrochloride boils at 98—102°C/1·5 Torr.

6,7-Dihydro-5*H*-benzocycloheptene (*X*)

A. *By dehydration of alcohol* II: By boiling the benzene solution of alcohol *II* (m.p. 100 to 101°C)[16,19] with a small amount of *p*-toluenesulfonic acid the desired product was obtained according to the literature[16] in a 90% yield: b.p. 73—75°C/1 Torr, $n_D^{28}$ 1·5837, $n_D^{20\cdot5}$ 1·5872.

B. *By a reaction of alcohol* II *with dimethylcarbamyl chloride*: To a solution of 8·1 g alcohol *II* in 7 ml pyridine a total of 5·5 g dimethylcarbamyl chloride was added dropwise and the mixture was refluxed for 7 h on an oil bath at 150°C. After cooling, the mixture was separated between ether and water, the ether solution was washed with dilute hydrochloric acid, with dilute sodium hydroxide and with water and, after drying with sodium sulfate, evaporated. The residue (7·9 g) yielded by distillation as the main product the hydrocarbon *X*, boiling at 68°C/0·8 Torr, $n_D^{25}$ 1·5851. For $C_{11}H_{12}$ (144·2) calculated: 91·61% C, 8·39% H; found: 91·48% C, 8·32% H.

C. *From chloride* III *with collidine*: The crude distillate (b.p. 66—80°C/0·5—1 Torr) obtained by the reaction of 120 g alcohol *II* with 68 ml thionyl chloride[18], was mixed with 50 ml 2,4,6-collidine, the mixture was diluted with 130 ml dioxane and the total was refluxed for 6 h. After evaporation of dioxane, the residue was dissolved in a mixture of benzene and ether, the solution was washed repeatedly with dilute hydrochloric acid and water and, after drying, it was distilled: 60·0 g, b.p. 74—76°C/1·5—2 Torr, $n_D^{21}$ 1·5863.

5-Formamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIX*)

18 g of hydrocarbon *X* were added to a mixture of 55 ml acetic acid and 9 ml concentrated sulfuric acid, followed by the addition of 20 g sodium cyanide under stirring at 3—10°C over a period of 40 min. In the course of further 20 min, a mixture of 14 ml acetic acid and 20 ml sulfuric acid was added dropwise, the mixture was stirred for 2 h at the given temperature and left overnight at room temperature. The mixture was then poured into 500 ml water and 150 g ice, the liquid obtained was neutralized by a solution of sodium hydroxide and extracted with a mixture of ether and benzene. By washing the extract first with dilute hydrochloric acid, then with 6% sodium hydrogen carbonate and finally with water, by drying and evaporation, a total of 13·3 g crude product was obtained which was purified by crystallization from a mixture of benzene and light petroleum: 7·81 g (34%), m.p. 171°C (benzene). UV spectrum (methanol): $\lambda_{max}$ 211 nm (log $\varepsilon$ 4·039). IR spectrum (Nujol): 770 (1,2-disubstituted benzene), 1662 (CONH—R), 3254 $cm^{-1}$ HCO—NH). For $C_{12}H_{15}NO$ (189·3) calculated: 76·16% C, 7·99% H, 7·40% N; found: 76·21% C, 7·96% H, 7·29% N. Khanna and coworkers[12] prepared the same compound by formylation of amine *XII* with chloral and reported its melting point as 165°C.

5-Methylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIII*)

A. Via *carbamate* XVIII: 8 ml of ethyl chloroformate were slowly added to a solution of 8·0 g amine *XII* in 20 ml benzene, the mixture was stirred for 30 min at room temperature, for 30 min at 60—70°C, and cooled. Filtration removed 2·34 g of the precipitated hydrochloride of amine *XII*

(m.p. 267—269°C). From the filtrate the remaining base was removed by washing and evaporation of the volatile fractions. A total of 11·2 g crude carbamate *XVIII* was obtained.

A solution of 10·0 g crude *XVIII* in 50 ml tetrahydrofuran was added to a solution of 6·0 g lithium aluminium hydride in 70 ml tetrahydrofuran, the mixture was refluxed for 6 h, after cooling it was decomposed with 24 ml of 20% sodium hydroxide, the precipitate was filtered, washed with tetrahydrofuran and the filtrate was evaporated. The crude product (6·8 g) was dissolved in 150 ml ether and, by adding an ether solution of hydrogen chloride, the corresponding *hydrochloride* precipitated: 7·8 g, m.p. 202—203·5°C (ethanol–ether). For $C_{12}H_{18}ClN$ (211·7) calculated: 68·07% C, 8·59% H, 6·61% N, 16·73% Cl; found: 67·87% C, 8·57% H, 6·65% N, 16·64% Cl. A *base* was liberated from the hydrochloride by alkalinization and was isolated by extraction with ether: b.p. 88°C/2 Torr. For $C_{12}H_{17}N$ (175·3) calculated: 7·99% N; found: 7·93% N.

B. *From the formamido derivative* XIX: The formamido derivative *XIX* (20·0 g) was reduced by 8 h of boiling with a solution of 9·0 g lithium aluminium hydride in 250 ml tetrahydrofuran. Isolation as previously yielded 15·2 g (85%) of the base, b.p. 85—88°C/1·5 Torr. The hydrochloride, m.p. 203—204°C (ethanol–ether). In a mixture with the hydrochloride of the product prepared according to *A*, it melts without depression. Khanna and coworkers[12] report for the hydrochloride a m.p. of 199—200°C.

5-Dimethylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXIII*)

A mixture of 5·0 g amine *XIII*, 3·3 ml 90% formic acid, 5·1 ml water and 5·5 ml 39% solution of formaldehyde was refluxed for 6 h. After cooling a mixture of 7 ml concentrated hydrochloric acid and 14 ml water was added and the liquid obtained was evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml water, the solution was washed with ether, filtered with charcoal and the filtrate was made alkaline with 20% sodium hydroxide. The product was isolated by extraction with ether: 4·56 g, b.p. 99—101°C/2 Torr. For $C_{13}H_{19}N$ (189·3) calculated: 82·47%C 10·13% H, 7·40% N; found: 82·40% C, 10·12% H, 7·37% N.

*Hydrochloride*, m.p. 224·5—225°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 6·20% N, 15·71% Cl; found: 69·05% C, 8·94% H, 6·26% N, 15·80% Cl. Khanna and coworkers[12] report for the compound prepared similarly from the primary amine a b.p. of 98—100°C/5 Torr, for the hydrochloride a m.p. of 218°C.

5-Acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XX*)

A mixture of 14·0 g amine *XII*, 50 ml benzene and 15 ml acetic anhydride was refluxed for 3 h and the volatile fractions were then evaporated under reduced pressure. The residue then yielded in the usual way the neutral product: 9·1 g, m.p. 208—209°C (60% ethanol). For $C_{13}H_{17}NO$ (203·3) calculated: 76·86% C, 8·43% H, 6·89% N; found: 77·08% C, 8·43% H, 6·85% N.

5-Ethylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIV*)

Amide *XX* (12·0 g) was boiled for 10 h with a solution of 12 g lithium aluminium hydride in 160 ml tetrahydrofuran, the mixture was decomposed after cooling with 50 ml 20% sodium hydroxide and processed similarly as in the case of the amine *XIII*. A total of 10·0 g crude *hydrochloride* was obtained which was crystallized from a mixture of ethanol and ether, m.p. 197—199°C. For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 6·20% N, 15·71% Cl; found: 69·33% C, 8.93% H, 6·18% N, 15·62% Cl. The *base* liberated in the usual way boils at 92°C/2 Torr. For $C_{13}H_9N$ (189·3) calculated: 82·47% C, 10·13% H, 7·40% N; found: 82·17% C, 10·03% H, 7·35% N.

5-Diethylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXIV*)

A mixture of 20 g diethylamine and 9·0 g crude chloride *III* (ref.[18]) was refluxed for 50 h, the excess diethylamine was evaporated and the residue divided in the usual way into a neutral and a basic fraction. The main product is the hydrocarbon *X*. The basic product *XXIV* (0·5 g) boils at 120°C/0·5 Torr. For $C_{15}H_{23}N$ (217·3) calculated: 6·45% N; found: 6·21% N.

5-(4-Methylpiperazino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXV*)

A solution of 12·5 g crude chloride *III* and 20 g 1-methylpiperazine in 50 ml chloroform was refluxed for 17 h. After evaporation of the chloroform the residue was divided between water and benzene and from the benzene fraction, a neutral and a basic product were isolated in the usual way. A total of 3·0 g *base* boiling at 144—146°C/2 Torr and melting at 54—55°C was obtained. For $C_{16}H_{24}N_2$ (244·4) calculated: 78·63% C, 9·90% H, 11·46% N; found: 78·56% C, 10·15% H, 11·56% N. Khanna and coworkers[12] obtained the compound in a similar way but as the only characteristic they report the m.p., of its picrate.

The *dihydrochloride*, m.p. 211—212°C in a capillary (ethanol–ether). For $C_{16}H_{26}Cl_2N_2 \cdot 0{\cdot}5\ H_2O$ (326·3) calculated: 58·91% C, 8·34% H, 8·58% N, 21·73% Cl; found: 59·42% C, 8·44% H, 8·50% N, 21·50% Cl.

5-(3,3-Diphenylpropylamino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XV*)

A mixture of 10·0 g 3,3-diphenylpropyl bromide[20], 10·0 g amine *XII* and 70 ml benzene was refluxed for 25 h. After cooling, the amine *XII* hydrobromide was filtered (3·0 g) and the filtrate was evaporated at reduced pressure. The residue was dissolved in 60 ml ether and the solution was extracted with 100 ml dilute hydrochloric acid (1 : 5). The precipitated *hydrochloride* of the product *XV* was filtered: 9·0 g, m.p. 219—221°C (ethanol). For $C_{26}H_{30}ClN$ (392·0) calculated: 79·68% C, 7·71% H, 3·57% N, 9·04% Cl: found: 78·97% C, 7·82% H, 3·61% N, 9·04% Cl.

1-(1-Naphthoxy)-3-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ylamino)-2-propanol (*XVI*)

A solution of 10·0 g 1-(1-naphthoxy)-2,3-epoxypropane[22] and 8·1 g amine *XII* in 50 ml ethanol was refluxed for 20 h. After evaporation of ethanol the residue was dissolved in 150 ml ether and, by treatment with an ether solution of hydrogen chloride, the *hydrochloride* was prepared (18·5 g), m.p. 222—224°C (ethanol). For $C_{24}H_{28}ClNO_2$ (397·9) calculated: 72·44% C, 7·09% H, 3·52% N, 8·91% Cl; found: 72·23% C, 7·05% H, 3·86% N, 8·92% Cl.

5-(Phenylacetamido)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXI*)

15·5 g phenylacetyl chloride was added under cooling to a solution of 16·1 g amine *XII* in 30 ml pyridine, the mixture was left for 24 h at room temperature, heated for 3 h to 70—80°C and after cooling poured into ice water. The precipitated product was filtered: m.p. 204°C (aqueous ethanol), For $C_{19}H_{21}NO$ (279·4) calculated: 81·68% C, 7·58% H, 5·01% N; found: 81·78% C, 7·77% H, 4·96% N.

5-(3,4,5-Trimethoxybenzamido)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXII*)

A solution of 23·1 g 3,4,5-trimethoxybenzoyl chloride in 120 ml benzene was added dropwise under cooling to a solution of 16·1 g amine *XII* in 50 ml pyridine, the mixture was left to stand for 3 h at room temperature, then was heated for 2 h to 50°C, the volatile fractions were evapor-

ated and the residue was mixed with water. A total of 10·0 g product precipitated, m.p. 213°C (aqueous ethanol). For $C_{21}H_{25}NO_4$ (355·4) calculated: 70·96% C, 7·09% H, 3·94% N; found: 70·70% C, 7·07% H, 3·86% N.

5-Phenylimino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IV*)

A mixture of 16·0 g ketone *I*, 10·0 g aniline, 0·2 g anhydrous zinc chloride and 35 ml toluene was refluxed for 7 h by using a water separator. After cooling, the mixture was filtered and the filtrate treated by distillation; 10·0 g (43%), b.p. 167—170°C/1 Torr. For $C_{17}H_{17}N$ (235·3) calculated: 86·77% C, 7·28% H, 5·95% N; found: 86·61% C, 7·29% H, 5·75% N.

5-Anilino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XVII*)

A solution of 26 g anile *IV* and 150 ml ether was added dropwise to a suspension of 14 g lithium-aluminium hydride in 150 ml ether. The mixture was refluxed for 6 h. After cooling it was decomposed by adding 56 ml 26% sodium hydroxide solution. The mixture was then filtered and the filtrate was treated by distillation; 18·8 g, b.p. 154—156°C/0·5 Torr, m.p. 82°C (hexane). For $C_{17}H_{19}N$ (237·3) calculated: 86·03% C, 8·07% H, 5·90% N; found: 86·28% C, 8·21% H, 5·90% N.

5-[N-(2-Dimethylaminoethyl)anilino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXVI*)

A mixture of 10·0 g amine *XVII*, 90 ml benzene and 2·2 g sodium amide was refluxed for 4 h. After cooling, 7·0 g 2-dimethylaminoethyl chloride was added and the mixture was refluxed under stirring for further 4 h. After cooling, it was decomposed with water, the benzene solution was evaporated and the residue chromatographed on a column of 250 g alumina. After separation of the less polar fractions by elution with light petroleum, elution with benzene yielded 6·5 g of the desired base, m.p. 76—77°C (hexane). For $C_{21}H_{28}N_2$ (308·5) calculated: 81·77% C, 9·15% H, 9·08% N; found: 82·02% C, 9·24% H, 9·16% N.

*Dihydrochloride*, m.p. 138—140°C (ethanol–ether). For $C_{21}H_{32}Cl_2N_2O$ (399·4) calculated: 63·15% C, 8·07% H, 17·75% Cl; found: 63·43% C, 8·22% H, 17·86% Cl.

5-(3-Dimethylaminopropyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (*V*)

A solution of 32 g ketone *I* in 100 ml benzene was added dropwise over a period of 30 min to a Grignard reagent[27] prepared from 5·84 g magnesium with 34 g 3-dimethylaminopropyl chloride in 60 ml tetrahydrofuran. The mixture was refluxed for 2 h. After cooling it was diluted with 150 ml ether, decomposed with a solution of 65 g ammonium chloride in 330 ml water, the organic layer was dried with solid potassium hydroxide and evaporated. Under cooling with ice, the residue was extracted with dilute hydrochloric acid and the solution of the hydrochloride yielded after alkalinization and extraction with ether a total of 15 g crude base.

Hydrogen maleate was prepared by neutralization of the crude base with maleic acid in a mixture of ethanol and ether; m.p. 126·5—128°C (ethanol–ether). For $C_{20}H_{29}NO_5$ (363·4) calculated: 66·09% C, 8·04% H, 3·85% N; found: 66·15% C, 8·13% H, 3·88% N.

5-(3-Dimethylaminopropylidene)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VI*)

A solution of 6·5 g crude base *V* in 20 ml concentrated hydrochloric acid and 80 ml water was heated for 20 min to 90°C, evaporated under reduced pressure to 20 ml, made alkaline

with 20% sodium hydroxide and the product was isolated by extraction with benzene; 5·4 g, b.p. 118—120°C/2 Torr. UV spectrum (methanol): $\lambda_{max}$ 242·5 nm (log $\varepsilon$ 3·932). Ref.[19] gives a maximum of absorption for analogous olefins with an exocyclic double bond at 241 nm, for those with an endocyclic double bond at 253 nm. IR spectrum (Nujol): 755, 772 (1,2-disubstituted benzene), 1 601 (Ar), 1 682 $cm^{-1}$ (C=C). For $C_{16}H_{23}N$ (229·4) calculated: 83·78% C, 10·11% H, 6·11% N; found: 83·51% C, 10·04% H, 5·73% N.

*Hydrogen maleate*, m.p. 76—79°C (ethanol–ether). For $C_{20}H_{27}NO_4$ (345·4) calculated: 69·54% C, 7·88% H, 4·06% N; found: 69·64% C, 7·80% H, 4·13% N.

5-Phenyl-5-(2-dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VIII*)

The base was prepared similarly as shown before[9], b.p. 170—171°C/0·5 Torr. IR spectrum (Nujol): 703 (monosubstituted benzene), 759 (1,2-disubstituted benzene), 1038 (ether), 1 600 $cm^{-1}$ (Ar). For $C_{21}H_{27}NO$ (309·4) calculated: 81·51% C, 8·80% H, 4·53% N; found: 81·64% C, 8·65% H, 4·58% N.

*Hydrogen maleate*, m.p. 88—89°C (ethanol–ether). For $C_{25}H_{31}NO_5$ (425·5) calculated: 70·56% C, 7·34% H, 3·29% N; found: 70·34% C, 7·30% H, 3·25% N.

5-Phenyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IX*)

A solution of 13·0 g 9-phenyl-6,7-dihydro-5*H*-benzocycloheptene[9,19,28] (*XI*) (b.p. 155—157°C/2 Torr, $n_D^{24}$ 1·6150, $\lambda_{max}$ 252 and 228 nm) in 150 ml ethanol was hydrogenated over Adams' catalyst made from 0·6 g platinum oxide under normal conditions on a shaker. After reaching a consumption of 1 450 ml hydrogen absorption was stopped, the catalyst was filtered off and the filtrate distilled: b.p. 130—132°C/0·7 Torr, $n_D^{21}$ 1·5830. The UV spectrum lost the absorption shown by the starting hydrocarbon *XI*. For $C_{17}H_{18}$ (222·3) calculated: 91·84% C, 8·16% H; found: 91·60% C, 8·50% H.

1-Phenyltetralin (*XXXII*)

2,5-Diphenylvaleric acid[29] (*XXVII*, 135 g, m.p. 76—78°C) was added at 100°C to polyphosphoric acid prepared in the usual way from 580 g phosphorus pentoxide and 370 ml 85% phosphoric acid. The mixture was heated for 90 min to 140—150°C. After cooling to 50°C it was poured into 4 kg of a mixture of water and ice and extracted with ether. The extract was freed of the nonreacted acid *XXVII* by washing with dilute sodium hydroxide (6·5 g acid *XXVII* were recovered) and evaporated; a total of 98 g oily mixture of neutral products was obtained. Distillation yielded 40·0 g of a fraction boiling at 134—136°C/1 Torr, $n_D^{22}$ 1·5987. IR spectrum (substance): 703 (monosubstituted benzene), 745 and 755 (1,2-disubstituted benzene), 1460 ($CH_2$), 1498 and 1630 (Ar), 2860 and 2930 ($CH_2$), 3020 $cm^{-1}$ (Ar). For $C_{16}H_{16}$ (208·3) calculated: 92·26% C, 7·74% H; found: 92·43% C, 7·70% H. Authentic 1-phenyltetralin, prepared by reduction of 1-phenyl-3,4-dihydronaphthalene with sodium in amyl alcohol[30], boils at 170°C/13 Torr and has an $n_D^{20}$ of 1·5913. Its IR spectrum is fully identical with the spectrum just described. Similarly, a comparison of the two substances by gas chromatography and by thin-layer chromatography on silica gel points to the conclusion that the two compounds are identical.

2,5-Diphenylvaleryl Chloride (*XXVIII*)

A mixture of 15·0 g acid *XXVII* and 18 ml thionyl chloride was heated for 3 h to 70—85°C. Excess thionyl chloride was evaporated and the residue distilled: 15·8 g (98%), b.p. 159—161°C/1

Torr. For $C_{17}H_{17}ClO$ (272·8) calculated: 74·84% C, 6·29% H, 13·00% Cl; found: 75·22% C, 6·34% H, 12·77% Cl.

2-Diethylaminoethyl 2,5-diphenylvalerate (*XXIX*)

A solution of 5·7 g 2-diethylaminoethanol in 50 ml benzene was added dropwise over a period of 10 min to a solution of 10·9 g chloride *XXVIII* in 80 ml benzene. The mixture was then refluxed for 2·5 h. The benzene was then evaporated, the residue dissolved in 100 ml dilute hydrochloric acid (1 : 10), the solution of the hydrochloride was washed with ether and excess sodium carbonate was added to liberate the base which was isolated by extraction with ether: 8·5 g, b.p. 185°C/1 Torr. For $C_{23}H_{31}NO_2$ (353·5) calculated: 78·15% C, 8·84% H, 3·96% N; found: 78·37% C, 8·90% H, 4·07% N.

*Hydrochloride*, m.p. 68—70°C (ethanol–light petroleum). For $C_{23}H_{32}ClNO_2$ (389·9) calculated: 70·84% C, 8·27% H, 3·59% N, 9·09% Cl; found: 71·12% C, 8·36% H, 4·00% N, 9·21% Cl.

N,N-Diethyl-2,5-diphenylvaleramide (*XXX*)

A solution of 10·9 g chloride *XXVIII* in 80 ml benzene was added dropwise over a period of 40 min to a solution of 8·0 g diethylamine in 50 ml benzene under external cooling and stirring. The mixture was stirred for another hour at room temperature, the precipitated diethylamine hydrochloride was then filtered (5·0 g) and the filtrate distilled: 10·5 g, b.p. 180°C/0·5 Torr. For $C_{21}H_{27}NO$ (309·4) calculated: 81·51% C, 8·80% H, 4·53% N; found: 81·46% C, 8·74% H, 4·83% N.

N-(3-Morpholinopropyl)-2,5-diphenylvaleramide (*XXXI*)

A solution of 17·0 g chloride *XXVIII* in 100 ml ether was slowly added to a solution of 10·2 g 3-morpholinopropylamine and 8·0 g triethylamine in 80 ml ether. The mixture was refluxed for 3 h. After cooling, the precipitated triethylamine hydrochloride was filtered and the filtrate evaporated to dryness. The residue was dissolved in dilute hydrochloric acid, the solution was washed with ether, filtered and the filtrate made alkaline with 20% sodium hydroxide. The liberated base was isolated by extraction with ether and, in a crude state, converted by neutralization with 6·0 g maleic acid in ethanol to a solution of hydrogen maleate, which was made to crystallize on adding ether: 20·6 g, m.p. 86—87°C (ethyl acetate–ether), For $C_{28}H_{36}N_2O_6$ (496·6) calculated: 67·71% C 7·31% H, 5·64% N; found: 67·84% C, 7·47% H, 5·73% N.

*Pharmacological screening was done at the unit of this institute at Rosice n/L. under the direction of Dr F. Hradil. Some of the compounds were evaluated in greater detail at the pharmacological department of this institute under the direction of Dr V. Trčka (circulatory effects) and of Dr J. Metyšová (neurotropic effects).*

*The analytical estimations were done at the analytical department of this Institute (headed by Dr J. Körbl) by Mr K. Havel, Mr M. Čech, Mrs J. Komancová, Mrs V. Šmídová, Mrs I. Vítová and Mrs A. Rychnovská. The spectra shown were recorded and interpreted in the physico-chemical laboratories of this institute under the direction of Dr E. Svátek and Dr B. Kakáč. The authors acknowledge the substantialhelp by Mr L. Tůma with the preparative part of the work described.*

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